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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/678,953 | 10/03/2000 | Hiroshi Kubota | 320727.50401. | 7343 |

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EXAMINER

TON, THAIAN N

ART UNIT

PAPER NUMBER

1632

DATE MAILED: 08/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|------------------------|---------------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 09/678,953 | KUBOTA ET AL. | |
| | Examiner | Art Unit | |
| | Thaian N. Ton | 1632 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 31 May 2005.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1,14 and 27-55 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1,14 and 27-55 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____ | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicants' Amendment and Response, filed 5/31/05, has been entered and considered. Claims 38 and 39 are cancelled; claims 14, 28, 40, 42, 43 and 49 have been amended; claims 1, 14 and 27-55 are pending and under current examination.

Response to Arguments

The prior rejection of claims 1-20 as being anticipated by Sargiacomo is to be overcome by Applicants' amendments to claims 14, 28 and 43 which cancel the term "progeny".

Double Patenting

The obviousness-type double patenting rejections of the claims 1, 14, 27-55 as being unpatentable over claims 1-20 of copending Application 10/358,325 and claims 1-30, 33, 27-30, 33, 35-46, 53-60 of copending Application No. 10/135,700 are withdrawn in view of Applicants' filing of terminal disclaimers. The disclaimers are found to be proper and have been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 14, 27-55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained for reasons of record advanced in the prior Office action, mailed 3/8/05.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Applicants argue that the claimed invention is enabled because the selection of the cells is based upon the expression of at least one ICAM antigen *and* lack of MHC class Ia antigen expression, and that this selection is sufficient to isolate bipotent hepatic progenitor cells. Applicants argue that the present inventors were first to fortuitously discover that the selection of cells based upon lack of MHC class Ia negative cells for ICAM expression isolates those progenitor cells of the paracemal (hepatic) lineage. Applicants point to the specification for support for this. Applicants argue that MHC class I negative cells *alone* do compromise this group of cells. However, the claimed invention is not to cells that are merely MHC class Ia negative. Rather, the claimed invention is directed to hepatic progenitors that are MHC class Ia negative *and* ICAM positive. In other words, the excerpt noted from the specification does *not* teach MHC class Ia negativity is *sufficient* to uniquely identify the bipotent progenitors, but merely states that the absence of the same marker is but one characteristic of hepatic progenitors. Thus, the three alleles of MHC notwithstanding, Applicants submit that the specific lack of MHC class Ia expression *coupled* with positive ICAM expression is sufficient to uniquely identify bipotent hepatic progenitors. See p. 8 of the Response.

These arguments have been considered, but are not persuasive. Page 10 of the specification, cited by Applicants, states that ICAM positive cells include hematopoietic, mesenchymal, and mature hepatic cells, and that MHC class I negative cells include bipotent hepatic progenitor cells, enucleated mature erythrocytes and an unidentified cell population. Thus, it is possible that, sorting

cells by these two markers alone (expression of ICAM-1 and lack of MHC class I) could result in, for example, a hematopoietic cell, such as an erythrocyte, as erythrocytes are hematopoietic cells. It is also possible that the cells in the "unidentified cell population" are cells that are also ICAM positive cells, and that, identification of the resultant cells would also have the instantly claimed characteristics. The flow chart, as pointed to by Applicants, has more steps than that result in merely sorting the cells by two markers, to result in bipotent hepatic progenitor cells. For example, there is a step to eliminate red blood cells, and further steps of isolation. The claimed invention is directed to a cell that expresses at least one ICAM antigen, and does not express MHC class Ia antigen and it is maintained that the recitation of these characteristics alone fails to attain the instant invention, which are bipotent hepatic progenitor cells.

Thus, it is maintained that the lack expression of MHC class I and expression of ICAM may not be sufficient to uniquely identify bipotent hepatic progenitor cells. Note further that MHC has three alleles, which are expressed throughout the population, thus, the lack of expression of class Ia may not, in itself, be sufficient to uniquely identify the bipotent hepatic progenitor cells. In view of the lack of teaching or guidance provided by the specification with regard to utilizing only particular markers to identify the bipotent hepatic progenitor cells, the teachings in the art to show that cells other than bipotent hepatic progenitor cells express the claimed markers, it would have required undue experimentation for one of skill in the art to practice the claimed invention.

Claims 1, 14, 27-55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time

the application was filed, had possession of the claimed invention. This rejection is maintained for reasons of record advanced in the prior Office action.

Applicants argue that adequate written description of the claimed invention can be found throughout the specification. For example, Applicants point to Example 6.4 to show hepatic cell suspensions stained for MHC class Ia and anti-ICAM1 could be sorted into discrete single-cell populations identifiable according to their respective staining pattern. Applicants argue that Example 6.6 provides evidence for the hepatic progenitor cells mentioned in Example 6.4. Applicants argue that the claimed invention has written description. Applicants point to a later published paper, which substantially teaches the claimed subject matter for evidence that this invention was sufficiently described and enabled for one of ordinary skill in the art to practice and understand the invention from the original disclosure.

This is not persuasive. The claims are directed to isolated single-cell bipotent hepatic progenitor cells. Broadly, the claims only require the expression of ICAM and lack of MHC class Ia expression. Example 6.4 teach that first teach staining for Anti-RTIA¹ and ICAM-1 antibodies, from which fractions are then isolated by FACS and screened for CFA for clonal growth potential in order to determine which fraction contain the hepatic cell populations. See p. 21, lines 4-8. These five fractions are then resorted and hepatic cell colonies are then identified by expression of albumin and alpha-fetoprotein. See p. 21, lines 9-10. Thus, it is clear from this example that the cells are firstly stained for ICAM and MHC class Ia expression, and then further sorted in order to identify which fraction contains the claimed cell populations. Note that the PNAS journal article has not been provided, which, the Examiner kindly reminds Applicants', is their duty to provide this art. However, to expedite prosecution, the Examiner has considered this piece of art. This article, as with the specification, teaches that cells were stained with alpha-fetoprotein and albumin, and then flow sorted by FACS and then screened for CFA.

The broadly claimed characteristics fail to uniquely identify the claimed bipotent hepatic progenitor. There is no specific description of a cell with expression of ICAM and lack of MHC class Ia as a bipotent hepatic progenitor cell, such that one skilled in the art would recognize that Applicants had possession of the claimed invention. Although the specification describes methods of isolating the hepatic progenitor cells, the characteristics of the cells require more than instantly claimed in order to describe the cells as hepatic progenitor cells.

The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described by the specification and which are not convention in the art at the time of filing. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that one of skill in the art would recognize that the inventor had possession of the claimed invention. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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